46. The method of Claim 38, wherein the anti-human CD23 monoclonal antibody comprises variable domains derived from 5E8, 6G5 or 2C8.

47. The method of Claim 38, wherein the disease condition is an allergic disorder.--

REMARKS

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, the non-elected claims have been canceled without prejudice or disclaimer to the subject matter thereof in order to expedite prosecution. As well, elected Claims 26-35 have been deleted and rewritten as new Claims 38-47, independent form the non-elected claims. All of the Claims now in the application (i.e., Claims 38-47) find support in the original claims et. seq.

Turning now to the Office Action, the Application was objected to for assertedly failing to comply with the requirements of 37 C.F.R. §§1.821 through 1.825 which relate to providing a listing for the sequences disclosed in the application in printed and computer readable form. By the amendment filed September 21, 2000, Applicants provided a copy of a "Sequence Listing", a computer readable copy of the "Sequence Listing" and a signed statement verifying

that the contents of the paper and the computer readable copies of the Sequence Listing are the same and that the submission contains no new matter. Thus, it believed that the objection has been obviated, and withdrawal thereof is therefore respectfully requested.

Applicants acknowledge the previous election with traverse of Claims 26-35, which are directed to therapeutic and prophylaxis methods based on the anti-human CD23 monoclonal antibodies of the invention. As noted above, in order to expedite prosecution, non-elected Claims 1-25, 36 and 37 are canceled herein. Therefore, the Restriction Requirement is now moot. As a result of the amendments to date, Claims 38-47 which are based on Claim 26-35 are now under consideration in the application , and all are directed to the elected subject matter.

Claims 26-35 (now Claims 38-46) stand rejected under 35 U.S.C. §112, first paragraph, as assertedly not being adequately enabled by the teachings of the subject application. The Office Action indicates that the disclosure only enables a method for preventing an IgE mediated immune allergy response with anti-CD23 in Abs [it should be noted that Claim 35 (now 47) relates to allergic conditions, and should not have been included in this rejection]. Apparently, the Examiner is of the opinion that the Specification does not sufficiently demonstrate that the subject monoclonal antibodies will possess treatment or prevention activity in relation to autoimmune or inflammatory conditions. This rejection is respectfully traversed for at least the following reasons.

Essentially, the position of the Examiner apparently is that the specification has not provided a link between inhibition of IgE expression in the SCID mouse model and the treatment of autoimmune or inflammatory conditions. In this regard, the Office Action alleges that the unpredictability of immunotherapeutics is evidenced by U.S. Patent No. 5,763,137, which indicates that *in vitro* functional assays cannot inherently predict the *in vivo* capability of a chimeric antibody to destroy or deplete target cells expressing a specific antigen. This reference has been considered. Essentially, the reference was relied upon to establish the art recognized complexity of treating immune systems disorders.

As discussed below, while Applicants acknowledge that there does exist some unpredictability in isolating and identifying an antibody to an unknown target, which possesses immunotherapeutic activity, Applicants respectfully submit that this unpredictability has been adequately rebutted based on the references discussed below which support the human clinical efficacy of anti-human CD23 antibodies.

One apparent concern of the Examiner is that the data obtained in SCID mice may not correlate to human efficacy. With respect to this issue, it is respectfully noted that many functional studies involving monoclonal antibodies in mice have correlated well to clinical studies in humans. Examples wherein mouse data has been extrapolated to human clinical trials include monoclonal antibodies to CD3, monoclonal antibodies to CD4, and monoclonal antibodies to TNF factor. In

all of these cases, functional effects seen in animal models have correlated into similar functional effects in humans. Therefore, Applicants respectfully submit it is reasonable to assume, absent evidence to the contrary, that the information obtained in the SCID mouse model should correlate to human clinical efficacy.

Moreover, the results reported in human clinical trials substantiate Applicants arguments that it is reasonable to conclude that the observed *in vitro* activity and *in vivo* data obtained in a SCID mouse model should correlate to human clinical efficacy.

Moreover, in the particular case of inflammatory diseases, it has been reported that a monoclonal anti-murine CD23 antibody (B3B4) blocks the establishment of collagen induced arthritis in mice. (Plater-Zyberk et al, *Nature Medicine*, Volume 1, No. 8, August 1995). The reference teaches marked amelioration of established collagen-induced arthritis by treatment with antibodies to CD23 *in vivo*. Moreover, the authors note that their findings demonstrate "the involvement of CD23 in a mouse model of human rheumatoid arthritis". Thus, it is further clear from the reference that this data was obtained in an art-recognized mouse model for a human inflammatory condition, i.e., rheumatoid arthritis.

It is hypothesized by an inventor of this application that the effect of the anti-CD23 antibody in this mouse model is probably attributable to blocking of the pro-inflammatory effects of soluble CD23. With respect thereto, the monoclonal anti-human CD23 antibodies disclosed in this application have been found to bind

to soluble CD23. Consequently, it is reasonable to expect that these antibodies will similarly block the pro-inflammatory effects of soluble CD23, and thereby inhibit inflammatory responses.

Accordingly, based on the foregoing, there is substantial evidence in the literature which substantiates the accepted therapeutic efficacy of antibodies that inhibit IgEs for treating human autoimmune diseases, and therefore why it is reasonable to assume that the data in this application will correlate to successful human therapy.

While it is acknowledged that the use of antibodies as therapeutic agents can be unpredictable, the predictability of the subject invention has been established. Indeed, Applicants respectfully submit that relevant evidence substantiating the efficacy of anti-CD23 antibodies are contained in the afore-described references, which demonstrate convincingly the accepted therapeutic efficacy of antibodies that inhibit IgE (including inflammatory and autoimmune conditions) for treatment of human diseases. Therefore, based thereon, it is reasonable to conclude that the results obtained in the SCID mouse model should correlate to effective human therapy.

Accordingly, in weighing the factors which are properly considered in determining whether practice of an invention would require undue experimentation, the weight of the analysis does not clearly favor a finding of undue experimentation.

Accordingly, based on the foregoing, withdrawal of the §112 enablement rejection in its entirety is respectfully requested. Essentially, based on the information of record and that provided herein, there exists substantial evidence which would allow one skilled in the art to reasonably conclude that the subject anti-human CD23 monoclonal antibody, which comprises a human gamma 1 constant domain, will provide a suitable therapeutic agent for treatment of human diseases including inflammatory and autoimmune conditions.

Claim 34 (now Claim 46) stand rejected under 35 U.S.C. §112, second paragraph as assertedly being indefinite for reciting domains derived from 5E8, 6G5 or 2C8. Essentially, the examiner is objecting to the recitation of those fragments without specific reference to deposited hybridoma accession numbers. This rejection is believed to be obviated by Applicants' Sequence Listing submission of September 21, 2000. Thus, withdrawal of the rejection is in order and respectfully requested.

Claims 26, 28-33 and 35 (now Claims 38, 40-45 and 47) stand rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Bonnefoy et al (WO 96/12741) as evidenced by Saxon et al (J. Immunol. Vol. 147 (11) 1991, pp 4000-4006). This rejection is respectfully traversed for at least the following reasons.

Bonnefoy et al does not disclose each feature of the subject invention. For example, Bonnefoy et al does not disclose a anti-human CD23 monoclonal antibody comprising human gamma-1 constant region. There is no indication in Bonnefoy et al of the therapeutic enhancements obtained in conjunction with providing an antibody including a human gamma-1 constant region as presently claimed. Moreover, as more extensively discussed below in connection with the obviousness rejection based on

Bonnefoy et al , this reference fails to recognize the advantages of employing a human gamma-1 constant region in connection with the therapeutic and prophylaxis methods of the invention. In this regard, it is noted that the Bonnefoy et al reference was before the Examiner in parent application Serial No. 08/803,085, now U.S. Patent No. 6,011,138. In the parent application, the Bonnefoy et al reference was cited by the Examiner in a 103 rejection which was withdrawn based on Applicants' arguments similar to those set forth below.

Thus, as discussed extensively below, Bonnefoy et al does not render the present claims obvious, much less anticipated. Accordingly, the rejection under 35 U.S.C. §102 based on Bonnefoy et al is improper and should be withdraw.

Claims 26-33 and 35 (now Claims 38-45 and 47) stand rejected under 35 U.S.C. §103(a) as assertedly being unpatentable over Bonnefoy et al in view of Saxon et al and Newman et al (U.S. Patent No. 5,658,570). This rejection is traversed for at least the following reasons.

Contrary to the Office Action, Applicants respectfully submit that the reference relied upon in the rejection, either alone or in combination, would not fairly teach or suggest the subject invention. For the reasons set forth below, these references separately or in combination fail to teach or suggest the gamma 1 constant domain containing antibodies of the present invention, or the enhanced results obtained thereby. This is because the references taken alone or in combination contain no disclosure which would indicate to one skilled in the art the potential benefit of the incorporation of a human gamma 1 constant domain on the ability of a particular antibody to human CD23 to inhibit IgE production. At best, the references taken in

combination would merely suggest that it would have been *prima facie* obvious to make chimeric antibodies from a murine antibody that inhibits IgE in order to reduce the immunogenicity thereof upon therapeutic administration. However, the reference would contain no suggestion as to which particular human constant domain to select, or any enhanced effect thereof on therapeutic activity. Moreover, based on what was known in the art relating to anti-CD23 antibodies, it would have been reasonably predicted that the particular constant domain would have little or no effect on activity. In this regard, and as disclosed in this application, it had been previously reported that a Fab_2, i.e., which lacks a constant region, is just as potent in inhibiting IgE production as a complete antibody. Thus, available information prior to the present invention would have suggested to one of ordinary skill that effector function was not significant to IgE inhibitory activity of anti-CD23 antibodies.

Thus, at best, the references would arguably suggest that the substitution of a human constant domain in favor of a murine constant domain in a murine antibody that inhibits IgE could result in an antibody having less immunogenicity when administered to humans. However, the references, separately or in combination, would not fairly suggest that any particular human constant domain in an anti-human CD23 antibody would have any significant effects on IgE inhibitory activity, especially based on the fact that a Fab fragment, i.e., which does not contain any constant domain, had been reported to be equally potent as a complete anti-human CD23 antibody.

By contrast, the present inventors have surprisingly discovered that the human gamma 1 containing anti-human CD23 antibodies of the present invention possess

substantially better activity than an otherwise identical anti-human CD23 antibody containing a human gamma 4 constant domain. More specifically, as discussed in the application, the gamma 1 version inhibited IL4-induced IgE production by B-cells, both *in vitro* and in a SCID mouse model much more effectively than the gamma 4 version. Moreover, the Fab_2 version containing the same variable regions was inactive. Therefore, the present inventors have surprisingly discovered that effector function is apparently highly significant to the therapeutic properties of the subject anti-human CD23 antibodies.

In fact, in view of the inventors' initial expectation, based on the previous literature, which suggested that the Fc effector function was not necessary for induced IgE inhibition, human gamma 4 versions of a subject antibodies were initially produced. However, as discussed at page 17 of the application, it was surprisingly found that the gamma 4 versions (produced from both of these primate monoclonal antibodies) were relatively ineffective, i.e., they required significantly higher concentrations (relative to gamma 1 version) in order to inhibit IL4-induced IgE production in *in vitro* assays. Moreover, it was surprisingly found that, when these same antibodies were later converted to human gamma 1 versions, i.e., by substitution of the primate constant domains with human gamma 1 constant domains, that they very effectively inhibited induced IgE production *in vitro*.

Therefore, the subject application contains convincing evidence as to the unexpected significance of the human gamma 1 constant domain on activity, which is not fairly suggested by the prior art. Indeed, the reasonable expectation, prior to the present invention, would have been that the incorporation of any particular human

constant domain would have little or no effect on IgE inhibitory activity, and that the only potential benefit would be reduced immunogenicity relative to an intact murine antibody. Accordingly, based on these unexpected results which are not fairly suggested by the prior art, withdrawal of the §103 rejection based on Bonnefoy taken in view of Saxon al and Newman et al is respectfully requested.

Moreover, even assuming *arguendo* that the above references rendered the claims *prima facie* obvious, the rejection should properly be withdrawn based on the unexpected results achieved by the subject invention. For the same reasons set forth above, the prior art would not fairly suggest that the selection of any particular human constant domain would be instrumental on the activity of an antibody specific to human CD23. Quite surprisingly, it has been found that the human gamma 1 constant domain has a significant effect on IgE inhibitory activity, in contrast to an otherwise similar antibody which contained a gamma 4 constant domain. These results would not have been fairly suggested based on the prior art, including the references relied upon in the Official Action.

In summary, all the prior art rejections should be withdrawn since the references separately or in combination fail to teach or suggest the particular selection of a human gamma 1 constant domain in a human anti-CD23 antibody or the enhanced results obtained thereby relative to anti-human CD23 antibody containing other human constant regions, or lacking a constant region altogether.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this reply, the Examiner is respectfully

requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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